REMARKS

Claims 1, 2, and 8-13 are currently pending in the application. Claims 1, 8, 10, and 12 are in independent form.

Claims 1-2 and 8-13 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for administering sildenafil or hMSC to ischemic rats, does not reasonably provide enablement for promoting neurogenesis in an ischemic patient in general by administering a phosphodiesterase type 5 inhibitor and cellular therapy. The Office Action holds that undue experimentation would be required to practice the invention.

Applicant reiterates that animal studies, and preclinical studies, form the basis for all drug research and development and the statements of the Office Action, likely, run counter to a myriad of patents. A Declaration is submitted in support of these arguments herein. Many treatments and drugs have been developed and first tested in the animal and subsequently moved to the human. This is an FDA requirement. This is a standard process that one skilled in the art recognizes. The mechanism of action shown in the rat studies is also present in human studies. Neurogenesis is present in the human after stroke (*PNAS August 29, 2006 vol. 103 no. 35 13198-13202 -among others)* and it was first demonstrated in rodent (A Arvidsson, et al. - Nature Medicine, 2002 - among many others). The mechanisms of action of sildenafil, a phosphodiesterase V inhibitor in the present invention, are the same as in the human. There is no reason to question the rat models of the present invention. They are directly predictive of results in humans, and one skilled in the art could practice the invention based on the studies shown in the specification.

Bjorklund, et al. is cited to show that cellular therapy in regard to treating ischemic stroke is not well settled in studies with rats. Bjorklund, et al. editorializes about the difficulty performing exogenously administered stem cell replacement studies in the rodent. Bjorklund, et al. states "without better knowledge of the biological mechanisms of improvement, and optimization of the functional outcome in animal models, cell therapy for patients with ischemic damage is unlikely to develop to a point of therapeutic value." There are a number of issues with this statement: 1) This is someone's OPINION, published 9 years ago, with no basis in fact; 2) The authors are not stroke experts, 3) They are discussing "cell replacement" therapies and not cell or pharmacological therapies that stimulate production of the brain's stem cells; and 4) Their statements are factually incorrect-there are excellent models of functional outcomes in animals, there have been major insights into mechanisms promoting improvement, and Applicant's laboratory as well as others have published extensively in this area. Thus, one skilled in the art would not regard the statements of Bjorklund, et al. as having relevance to the subject matter of the present invention.

The Office Action holds that the claims are very broad insofar as they suggest that neurogenesis can be promoted by administering phosphodiesterase type 5 inhibitors and cellular therapy in general. Applicant notes that the group of phosphodiesterase type 5 inhibitors encompasses a well-defined group, and one skilled in the art would expect one PDE5 inhibitor would function in the same manner as another. Applicant has amended the claims to define cellular therapy as mesenchymal stem cells, without prejudice. While many types of cellular therapy would function in the same manner as mesenchymal stem cells, the examples of the present invention are directed to mesenchymal stem cells, and therefore there is direct support for this type of cellular therapy in combination with a PDE5 inhibitor in the specification.

The Office Action holds that more guidance is required to treat humans with the method disclosed, and cites Johansson to show that regeneration of transectioned central axons have never been convincingly demonstrated in higher mammals and that recovery from stroke seen in humans is likely due to reorganization of cortical networks, and that recovery after stroke is time sensitive. Therefore, the Office Action holds that it is doubted that neurogenesis can be promoted in humans by simply administering a PDE 5 inhibitor and cellular therapy.

These comments of Johansson, as noted above for Bjorklund, are not data, but opinions provided in a recorded lecture. These comments do not in anyway preclude Applicant's ability to stimulate recovery of function using cells of drugs (e.g. PDE5 inhibitors). Transected axons are irrelevant to stroke. Applicant and others have shown that axons can be stimulated to grow in the central nervous system (J Cereb Blood Flow Metab. 2008 Aug;28(8):1440-8. Epub 2008 Apr 16, *Stroke.* 2008;39:2571;The Journal of Neuroscience, July 7, 2004, 24(27):6209-6217; among others). The statement that recovery is likely the result of retraining brain, does not in anyway preclude Applicant's ability to stimulate and enhance this recovery. The comment by the Office Action that recovery from stroke is time sensitive, does not in anyway preclude treatment to enhance recovery. Nor does Applicant propose that treatment is time independent. Applicant has shown that the treatments of the present invention (MSCs, PDE5 inhibitor) provide functional benefit even when therapy is initiated one month post stroke. Applicant does not claim that these treatments will be effective when initiated at all times, e.g. 5 years post stroke. The Office Action also holds "given that central axons have never been convincingly demonstrated and that recovery is time sensitive, it is doubted that neurogenesis can be promoted in humans by simply administering a PDE5 inhibitor and cellular therapy." The logic of this statement is irrational. It is a non-sequitor. In addition, the statement counters the best available scientific evidence that cellular and certain

drug therapy promote neurogenesis in the laboratory. Applicant has no basis as noted above to preclude this from occurring in the human, and all evidence suggests that neurogenesis occurs in the human and the biology of the human and the animal are similar. If one would follow the "logic" of the Office Action, there would be no science.

Since the specification is fully supportive for promoting neurogenesis in an ischemic patient by administering a phosphodiesterase type 5 inhibitor and cellular therapy of mesenchymal stem cells, reconsideration of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1, 8, 10, and 12 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,043,223 to Black in view of Yoshimura, et al. Specifically, the Office Action holds that Black discloses a method of treating abnormal brain tissue as a result of ischemia in a mammal by administering bradykinin and a cGMP specific phosphodiesterase inhibitor zaprinast (type V inhibitor). The Office Action holds that since the same compound is being administered to the same patient as instantly claimed, the method of Black would be expected to inherently possess the same properties such as promoting neurogenesis to a limited extent. Black does not teach identifying numbers of new neurons. Yoshimura, et al. teaches that FGF-2 promotes neurogenesis after head injury, that mammalian neuroprogenitor cells in the adult brain can proliferate and differentiate into neurons after brain injury, identifying neuronal growth via BrdU labeling and NeuN expression. Yoshimura, et al. does not teach administration of a phosphodiesterase type 5 inhibitor. Therefore, the Office Action holds that it would have been obvious for one skilled in the art to have identified numbers of new neurons, since head injury is often associated with memory loss and regaining memory post treatment would be a way of identifying increased numbers of

new neurons. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over Black in view of Yoshimura, et al. is respectfully requested.

"Any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"; however, that reason must be present for the combination to be obvious. *KSR Intern Co. v. Teleflex*, 127 S. Ct. 1727, 1742, U.S. (2007). This requirement was confirmed in *Takeda Chem. Indust., et al. v. Alphapharm*, No. 06-1329 (Fed. Cir. 2007).

Black addresses a method to increase the permeability of brain capillaries, to open the blood brain barrier for delivery of pharmacological agents to abnormal tissue (stated explicitly throughout the patent). This is completely irrelevant to the present invention. Opening of the blood brain barrier to deliver an agent has nothing to do with neurogenesis nor is it a restorative treatment for a neural injury. Black discloses opening the blood brain barrier as simply a way to deliver agents which normally do not cross the blood brain barrier. Actually, opening the blood brain barrier is dangerous and increases damage to the brain after stroke or traumatic brain injury. One wants to close the blood brain barrier after stroke to regain the integrity of the capillary system. There is no scientific or logical connection between the present invention and the Black patent. Black is also very specific about "opening brain capillaries" and using a combination of bradykinin and a cGMP inhibitor to open the capillaries. The delivery of the restorative agents of the present invention are also independent of the opening of the blood brain barrier, since Applicant has shown that delivery performed one month after stroke provides functional benefit. The statement by the Office Action that the methods of Black could promote neurogenesis is a logical flaw. Black specifically notes the intention of opening the blood brain barrier to deliver agents, a pathophysiological event that is

disconnected from the generation of new neurons. There is no basis in logic or scientific literature by which anyone can make the connection between delivery of drugs, opening the blood brain barrier and the induction of new brain cells. Therefore, Black neither discloses nor suggests the critical steps of the present invention of promoting neurogenesis nor increasing neurological function, and therefore, there would be no possible way to identify new neurons nor any reason to try identifying new neurons, because such neurons are not present in Black. Thus, there would be no reason to look to Yoshimura, et al. in order to identify numbers of new neurons.

Furthermore, Yoshimura, et al. does not disclose the compounds of the present invention but rather FGF-2. FGF-2 was shown to increase neurogenesis in a specific region of the brain, the hippocampus. Different therapeutic agents affect different parts of the brain. There is no reason to believe that the compounds in Black would function in the same manner as those in Yoshimura, et al. In fact, the compounds of the present invention promote neurogenesis in the subventricular zone, a much different region of the brain than the hippocampus, as well as the hippocampus, and thus the compounds of the present invention promote functional benefits that cannot be derived from FGF-2 as in Yoshimura, et al.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 2, 9, 11, and 13 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,043,223 to Black as applied to the claims above,

and in view of Labat. Specifically, the Office Action holds that Black does not teach further including cellular therapy. Labat teaches the use of stem cells for managing neurological disorders such as stroke, brain trauma, and Parkinson's. Therefore, the Office Action holds that it would have been *prima facie* obvious for one skilled in the art to have combined the composition of Black with the stem cells of Labat, since they are both useful for treating head trauma or stroke.

As stated above, Black does not disclose all of the required elements of the independent claims, i.e. promoting neurogenesis/increasing neurological function and identifying increased numbers of new neurons. Combining Black with Labat does not make up for these deficiencies. Furthermore, Labat merely teaches that there are sources of adult stem cells in many areas of the body. Labat does not teach that adult stem cells can stimulate recovery of function and amplify the endogenous production of brain stem cells that contribute to recovery of function. Labat specifies throughout the article that the objective of stem cells is "replacing lost or worn out cells." Furthermore, the present invention provides unexpected results with respect to the combination of a PDE5 inhibitor and cellular therapy of MSCs. The combination treatment results in a synergistic effect of the individual components, and therefore, lower doses of each can be administered to patients. This limits the side effects or harmful effects that one taking each component at a normal dose would experience. See paragraph [0034], and the examples. This allows for more patients to be able to take such therapy wherein the past side effects could render them ineligible for treatment. Therefore, combining Black and Labat does not arrive at the present invention with regards to either the independent or dependent claims.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the

combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 1, 8, 10, and 12 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-8, and 14-17 of copending Application No. 10/075,715, and claims 1, 6, and 7 of copending Application No. 10/018,201. As noted in the Office Action, these rejections can be readily overcome by the filing of a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) or (d). Applicant stands ready to provide the appropriate terminal disclaimer upon the indication of the allowance of the pending claims.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

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I hereby certify that this correspondence is being electronically filed with the United States Patent & Trademark Office on the above date.

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